REMARKS

Claims 34-39 are pending in this application. Claims 1-33 were previously cancelled.

Claims 34, 35 and 38 are currently amended. Support for the amendments can be found in the Substitute Specification at page 20, lines 12-13, and Examples 1-3, beginning on page 21, reciting generation of an expression construct, cell transfection with the expression construct, and purification of the mature antibodies from the supernatant.

No new matter has been added.

35 U.S.C. §112 Written Description

The Examiner rejects claims 34-39 under 35 U.S.C. § 112 as not being supported by adequate written description.

The Examiner asserts that:

> It is not well established in the art that an antibody encompassed by the claims is amenable to the extent and degree of the modifications to the Fc or constant domain that would allow proper folding and assembly of the antibody, and the Specification is not any more enabling for producing a functional, immunogenic antibody that meets all of the claim limitations (Office Action, page 5).

In particular, the Examiner appears concerned that not all structures would properly fold and that the glycosylation in the IgG2a area could be variable or possibly interfere with the folding of the antibody (Office Action, page 5 and page 8).

Applicants respectfully submit that the Specification and knowledge in the art at the time of filing amply support the presently claimed antibodies and antibody fragments by providing the structure of the antibody or antibody fragments, in particular that of SEQ ID NO: 2, 3, 4, and 5, the structure of the IgG2a constant region, and the locations of hamster and primate glycosylation.

The claims recite a specific structure which the antibody fragment must include, i.e., an antibody comprising a protein sequence secreted from a cell comprising an expression vector including a DNA encoding at least one of SEQ ID NO: 2, 3, 4, or 5, at least a part of the murine IgG2a subtype amino acid sequence, and hamster or primate glycosylation. This structure is taught in the Specification and is supported by the knowledge in the art at the time of filing.

As a preliminary matter, Applicants point out that the antibodies and antibody fragments of the present invention are not required to function as antibodies *per se*. Instead, they are injected as a vaccine, and are intended to function as antigens. The Specification indicates that antibodies can be used as "substitutes for the antigen from which they have been derived" (Specification, page 4).

It is clear that the structures are provided for SEQ ID NO: 2, 3, 4, and 5, as obviously the amino acid sequence is listed in the sequence listing. SEQ ID NO: 2, 3, 4, and 5 are specific chains from a recombinant anti-EPCAM antibody with a modified sequence. Moreover, the DNA encoding these sequences would have been recognized by one of skill in the art due to the degeneracy of the genetic code.

With regard to the murine IgG2a subtype amino acid sequence, the murine IgG2a structure was known in the art at the time of filing. *See* Substitute Specification, page 12, lines 13-14, referring to the IgG2a sequence in Sun et al., Proc Natl Sci USA, 84:214-8 (1987), in Specification as originally filed, page 11, beginning at line 12. See also, page 8, line 36 (found in Original Specification beginning at page 7, last line) referring to Schnieder et al (Proc Natl Acad Sci USA 85:2509-13 (1988) which speaks of genetically engineered structural features having a relatively flexible structure. Moreover, the preferred location of the IgG2a sequence is disclosed, specifically at page 15, lines 10-15 of the Substitute Specification. Thus, one of skill in the art would know a) the sequence to switch out, and b) where to switch out the sequence.

With regard to the glycosylation, Applicants submit that the glycosylation itself, and the points in the antibody or antibody fragment where the glycosylation would attach are described in the Specification as being known in the art:

> The IgG2a immunogenic antibody is produced by genetic engineering as a recombinant molecule. Suitable host cells are CHO . . . cells, BHK . . . cells, HEK . . . cells, or the like. In any case the translated antibody thus obtains the glycosilation pattern of the host cell, which is critical to the immunogenicity of the antibody. . . .
>
> Specific host cells may be selected according to their capability to produce a glycosylated expression product. Host cells could also be modified to produce those enzymes that are required for specific glycosylation (Glycoconj. J. (1999), 16: 81) (Substitute Specification, page 17, lines 24-38).

Therefore, not only were the glycosylation patterns generally known in the art, but modifications to obtain specific glycosylation patterns were known in the art at the time of filing. This is supported by the knowledge in the art as evidenced by papers which were published well before filing. For instance Jefferis *et al.*, 1995, "Recognition sites on human IgG for Fcγ receptors: the role of glycosylation," Immunology Letters 44:111-117 (abstract attached), published eight years before the foreign priority date of the present application, demonstrate that N-linked carbohydrates generally attach to antibodies expressed in mammalian cells at the sequence NST.

Accordingly, the Examiner's assertion that the Specification does not identify even a partial structure is clearly in error.

Additionally, Applicants submit that they have identified physical and chemical characteristics which are coupled with correlation between structure and function for the genus of the immunogenic antibody. Both complete and partial antibody structure and the associated function of each part of the antibody structure was well-known at the time of filing. The application of these functional features to an entire antibody and to a partial antibody would be routine to one of skill in the art.

For instance, the claimed antibody sequences recite heavy or light chains. (See Substitute Specification, page 12, lines 9-14, 16-21, and 23-26 and Figures 6, 7, 8, and 9). As antibody chains of an anti-EpCam antibody, they would be expected to have at least some of the antigenic features of the complete anti-EpCam antibody, such as antigenic linear epitopes which are found in the complete antibody. These linear epitopes would be expected to be present even

when there is not complete folding of the antibody, because they depend primarily on the order of the amino acid sequence. Furthermore, Applicants demonstrate that an anti-idiotypic antibody was generated with Fab2 fragments from mAb17A, thus, these fragments were immunogenic (Substitute Specification, page 23, 32-34). Thus, Applicants submit that the antibody fragments of the invention would be expected to function in a manner similar to that shown in Example 8.

Similarly, the IgG2a portion is described as having particular areas which add immunogenicity to an antibody. The IgG2a hinge region is described as having a mimotope of EpCAM, triggering a response to the tumor associated antigen EpCAM (Substitute Specification, page 14, 3-9 and lines 13-17), thus is particularly immunogenic. In addition, the Specification points to regions in the antibody where the IgG2a portions are inserted (Substitute Specification, page 15, lines 10-15). Thus, Applicants have connected the IgG2a structure to an immunogenic structure.

Accordingly, Applicants submit that the Specification adequately teaches the structure of the claimed antibodies or antibody fragments which would be expected to be immunogenic, i.e., the structure which is coupled to the immunogenic function. Therefore the present claims are fully supported by written description.

Applicants also point out that they have provided working examples demonstrating the efficacy of the claimed antibody. The Examiner concedes that the Specification provides at least one example of the hybrid immunogenic antibody in Figure 4 and Example 8 (Office Action, page 5).

For this additional reason, Applicants request that the written description rejection be withdrawn.

As an aside, the Examiner appears concerned that the art suggests there would not be proper folding of the antibody. Applicants note that this is primarily an enablement concern, as they have discussed above how the Specification points to particular parts of the IgG2a isotype sequence and to knowledge of the content and binding methods of glycosylation both of which

have been described in the Specification to lead to immunogenicity, thus, demonstrating possession of the claimed genus of antibodies and antibody fragments. Applicants accordingly address this concern below with regard to the enablement rejection.

Rejections Under 35 U.S.C. § 112, Enablement

The Examiner rejects claims 34-39 35 U.S.C. § 112, as not being enabled. Applicants respectfully traverse.

The Examiner states:

> It is not well established in the art that an antibody encompassed by the claims is amenable to the extent and degree of the modifications to the Fc or constant domain that would allow proper folding and assembly of the antibody, and the Specification is not any more enabling for producing a functional, immunogenic antibody that meets all of the claim limitations (Office Action, page 5).

Applicants herein provide the Declaration of Dr. Manfred Schuster, one of the present inventors, which explains why one of skill in the art would have understood how to make and use the claimed invention without undue experimentation based on the teachings of the Specification and the knowledge in the art at the time of filing.

Dr. Schuster points out that the antibodies of the present invention are not being used for their antibody function per se, but are instead used as antigens (Schuster Declaration, page 3). Dr. Schuster points out that both linear epitopes and conformational epitopes(three-dimensional epitopes) based on the "foreign" murine sequences are present in a properly folded antigen. Thus, "the presentation of these linear epitopes elicits as consequence a humoral and cellular immune response" (Schuster Declaration, page 3). Accordingly, the Examiner's concerns regarding proper folding and assembly do not reflect the understanding of one of skill in the art at the time of filing, and therefore are improper.

Additionally, Dr. Schuster provides *in vivo* primate data demonstrating the immunogenicity of an antibody of the present invention comprising a protein sequence secreted from a cell comprising an expression vector including a DNA encoding at least one of SEQ ID

NO: 2, 3, 4, and/ or 5, at least a part of the murine IgG2a subtype amino acid sequence, and hamster or primate glycosylationwhich is comparable to the monoclonal mAb17-1A (Declaration, page 4). Dr. Schuster points to the nature of the antibody being a murine IgG2a isotype as contributing to its immunogenicity, "since the human antibody repertoire does not contain this very special isotype for rodent species" (Schuster Declaration, page 4).

Furthermore, Dr. Schuster comments that one of skill in the art would have known "where the non-human mammalian glycosylation would attach and that it would enhance the immunogenicity of the antibody or antibody fragment" based on the earlier published Jefferis et al. paper.

Thus, Applicants submit that one of skill in the art would have understood how to make and use the claimed antibodies without undue experimentation based on the Specification and the knowledge of one of skill in the art at the time of filing. Applicants request that the rejection be withdrawn.

Applicants also respectfully disagree with the Examiner's statement that it was not established in the art that the antibodies of the claims would allow proper folding an assembly of the antibody. As discussed above, to a certain degree proper folding is not necessary for an antibody to be immunogenic. However, the Specification also particularly addresses how to avoid mis-folding of an antibody by providing solutions such as bicistronic expression vectors, particular selection of cell lines for transfection, and control of expression using strong promoters (Substitute Specification, page 7, lines 17-21 and page 7, line 32 to page 8, line 7). The Examiner has provided no evidence for suggesting that improper folding would be a concern or would make one of skill in the art believe that an antibody or fragment thereof would suddenly become non-immunogenic.

For this additional reason, Applicants request that the rejection be withdrawn.

CONCLUSION

In view of the above response, Applicants believe the pending application is in condition for allowance and respectfully request withdrawal of the present rejections.

Pursuant to 37 C.F.R. §§ 1.17 and 1.136(a), Applicants respectfully petition for a four (4) month extension of time for filing a reply in connection with the present application, and the required fee of $865.00 is attached hereto.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact the undersigned at the telephone number below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37.C.F.R. §§1.16 or 1.14; particularly, extension of time fees.

Dated: March 24, 2011

Respectfully submitted,

By: _____

Leonard R. Svensson
Registration No.: 30,330
BIRCH, STEWART, KOLASCH & BIRCH, LLP
12770 High Bluff Drive
Suite 260
San Diego, California 92130
(858) 792-8855
Attorney for Applicants

Attachments: Jefferis *et al.* Abstract
Declaration of Dr. Manfred Schuster